

AMENDMENT AND RESPONSE TO OFFICE ACTION

Title: Synthesis of Combretastatin A-4 Prodrugs and Trans-Isomers Thereof

U.S. Patent Application Serial No. 09/582,950

Attorney Docket No. 12504.355

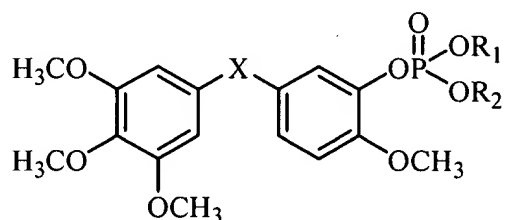
**AMENDMENTS TO THE CLAIMS:**

The following is a complete listing of the claims.

Claims 1-10 (Cancelled)

11. (Previously presented) A process for preparing a compound of Formula III,

(III)



wherein:

X represents a *cis* or *trans* alkenyl group represented by  $-(CH=CH)_1-$ ;

one of  $-OR_1$  or  $-OR_2$  is  $O^-Q^+$  or  $-O-Q$ , and the other is hydroxyl,  $-O^-Q^+$ , or  $-O-Q$ ; and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

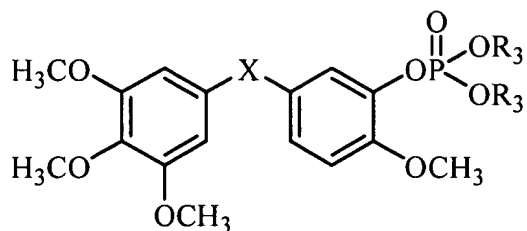
a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with a di(arylmethyl)phosphite in the presence of a tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula I,

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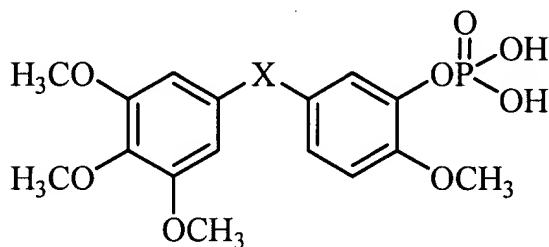
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(I)

wherein  $\text{R}_3$  is an arylmethyl phosphate protecting group; and

b) contacting the protected phosphate ester of Formula I with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II.



(II)

and

c) converting the phosphoric acid compound of Formula II into the compound of Formula III.

12. (Previously presented) The process of claim 11, wherein the phosphoric acid compound of Formula II is contacted with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition

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metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula III.

13. (Previously presented) The process of claim 11, wherein the phosphoric acid compound of Formula II is contacted with sodium methoxide to generate a disodium phosphate salt or a monosodium phosphate salt of combretastatin A-4.
14. (Previously presented) The process of claim 11 wherein the di(arylmethyl)phosphite is dibenzyl phosphite.
15. (Previously presented) The process of claim 11 wherein the tetrahalomethane is selected from the group consisting of CCl<sub>4</sub>, CBr<sub>4</sub>, CF<sub>4</sub>, and Cl<sub>4</sub>.
16. (Previously presented) The process of claim 11 wherein the tertiary amine is selected from the group consisting of N,N-diisopropylethylamine, triethylamine, pyridine, N-methyl morpholine, and DBU.
17. (Previously presented) The process of claim 11 wherein the acylation catalyst is N,N-dimethylaminopyridine.

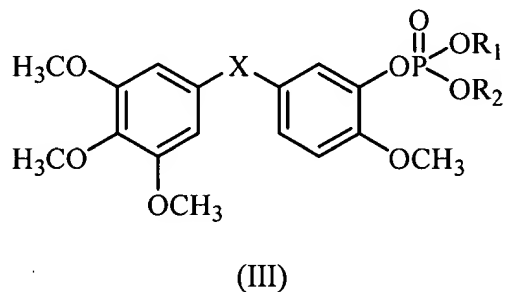
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18. (Previously presented) The process of claim 11 wherein the trialkylhalo silane is selected from the group consisting of trimethylbromo silane, trimethylchloro silane, trimethyliodo silane, trimethylfluoro silane, and mixtures thereof.
19. (Previously presented) The process of claim 11 wherein the solvent is a halogenated or non-halogenated solvent.
20. (Previously presented) The process of claim 19 wherein the solvent is acetonitrile.
21. (Previously presented) The process of claim 11, wherein Q is selected from the group consisting of calcium, cesium, lithium, sodium, magnesium, manganese, and zinc.
22. (Previously presented) A process for preparing a compound of Formula III,



wherein:

X represents a *cis*- or *trans*- alkenyl group represented by  $-(CH=CH)_1-$ ; and

$R_1$  and  $R_2$  are hydrogen;

the process comprising:

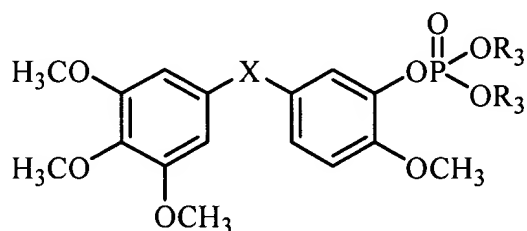
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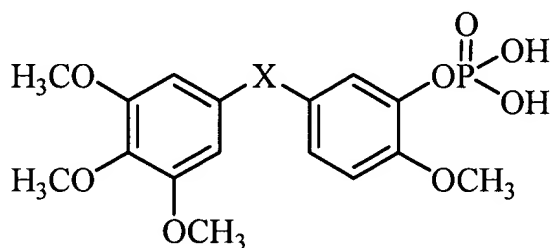
a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with a di(arylmethyl)phosphite in the presence of a tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula I,



(I)

wherein  $\text{R}_3$  is an arylmethyl phosphate protecting group; and

b) contacting the protected phosphate ester of Formula I with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II.



(II)

and

c) converting the phosphoric acid compound of Formula II into the compound of Formula III.

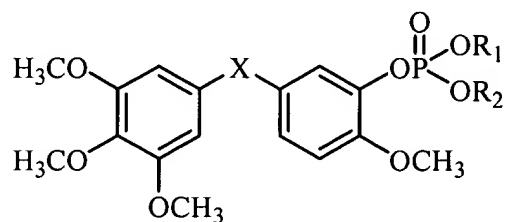
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23. (Currently amended) A process for preparing a compound of Formula III,



(III)

wherein:

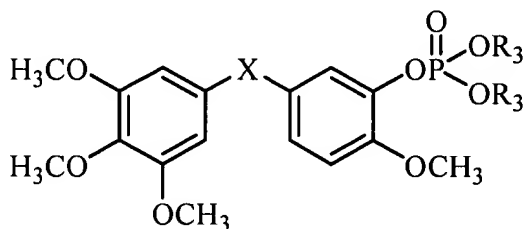
$\text{X}$  represents a *cis*- or *trans*- alkenyl group represented by  $-(\text{CH}=\text{CH})_1-$ ;

one of  $-\text{OR}_1$  or  $-\text{OR}_2$  is  $\text{O}^-\text{Q}^+$  or  $-\text{O}-\text{Q}$ , and the other is hydroxyl,  $-\text{O}^-\text{Q}^+$ , or  $-\text{O}-\text{Q}$  and

$\text{Q}$  is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

- (a) contacting *cis*- or *trans*-combretastatin A-4 in a solvent with 1*H*-tetrazole, a phosphine, and an oxidizing agent at a temperature for a period of time sufficient to form a protected phosphate ester of Formula I,



(I)

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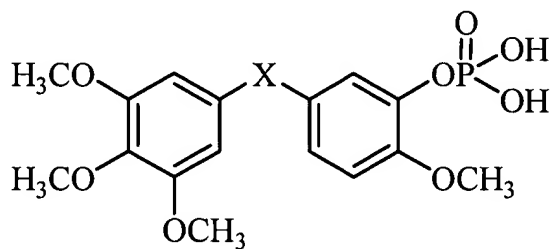
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wherein  $R_3$  is an aryl, arylmethyl or alkyl phosphate protecting group; and

(b) contacting the protected phosphate ester of Formula I with ~~an acidic compound or a~~ trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula II,



(II)

and

(c) converting the phosphoric acid compound of Formula II into the compound of Formula III.

24. (Previously presented) The process of claim 23, wherein the phosphoric acid compound of Formula II is contacted with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula III.
25. (Previously presented) The process of claim 23, wherein the phosphine is selected from the group consisting of di-tert-butyloxy(N,N-diethylamido)phosphine, di-tert-

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butyloxy(N,N-diisopropylamido)phosphine, bis-[2-(trimethylsilyl)ethoxy]-N,N-diisopropylamidophosphine, and dibenzyl-N,N-diethylphosphoramidite.

26. (Previously presented) The process of claim 23, wherein the oxidizing agent is selected from the group consisting of mCPBA, hydrogen peroxide, t-butyl hydroperoxide, and peroxyacids.
27. (Previously presented) The process of claim 23 wherein the temperature is about  $-70^{\circ}\text{C}$  to about  $25^{\circ}\text{C}$ .
28. (Previously presented) The process of claim 23 wherein the solvent is a halogenated solvent, a non-halogenated solvent, or a mixture thereof.
29. (Previously presented) The process of claim 28 wherein the solvent is a mixture of tetrahydrofuran and dichloromethane.
30. (Previously presented) A process for preparing a compound of Formula VI

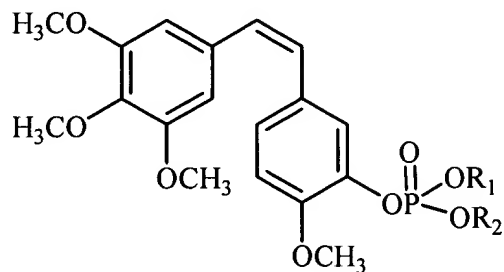


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(VI)

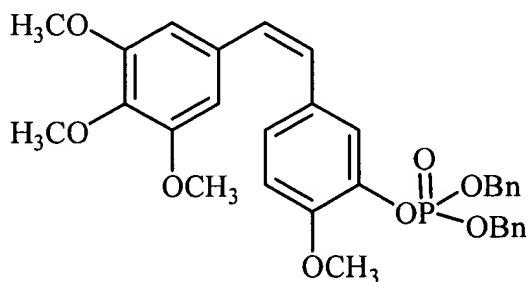
wherein,

one of -OR<sub>1</sub> or -OR<sub>2</sub> is O<sup>-</sup>Q<sup>+</sup> or -O-Q, and the other is hydroxyl, -O<sup>-</sup>Q<sup>+</sup>, or -O-Q and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic,

the process comprising:

(a) contacting *cis*-combretastatin A-4 in a solvent with di(benzyl)phosphite in the presence of tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula IV;



(IV)

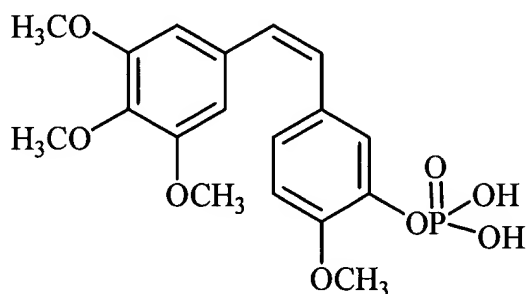
(b) contacting the protected phosphate ester of Formula IV with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula V; and

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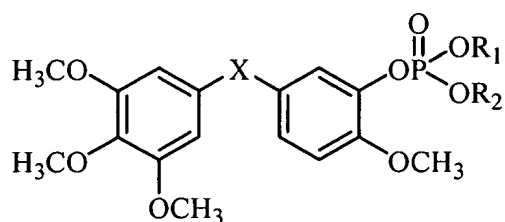


(V)

(c) contacting the phosphoric acid compound of Formula V with an alkali metal hydroxide, alkali metal alkoxide, alkali earth metal hydroxide, alkali earth metal alkoxide, transition metal hydroxide, transition metal alkoxide, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or a salt thereof to generate a compound of Formula VI.

31. (Previously presented) A compound of Formula III,

(III)



wherein:

X represents a *cis*- or *trans*- alkenyl group represented by  $-(CH=CH)_1-$ ;

one of  $-OR_1$  or  $-OR_2$  is  $O^-Q^+$  or  $-O-Q$ , and the other is hydroxyl,  $-O^-Q^+$ , or  $-O-Q$ ; and

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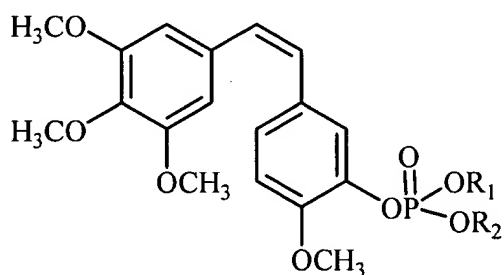
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Q is an alkali metal other than sodium or potassium, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, a nitrogen-containing antibiotic, or any combination thereof.

32. (Previously presented) The compound of claim 31, wherein Q is selected from the group consisting of cesium, lithium, magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc, platinum, silver, gold, imidazole, pyridine, pyrazole, morpholine, piperidine, piperazine, adenosine, tetracycline and verapamil, cinchonine, glucosamine, quinine and guanidine.

33. (Currently amended) A compound having a general structure of the formula VI:



(VI)

wherein:

one of  $-\text{OR}_1$  or  $-\text{OR}_2$  is  $\text{O}^-\text{Q}^+$  or  $-\text{O}-\text{Q}$ , and the other is hydroxyl,  $-\text{O}^-\text{Q}^+$ , or  $-\text{O}-\text{Q}$ ; and

Q is an alkali metal other than sodium or potassium, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an

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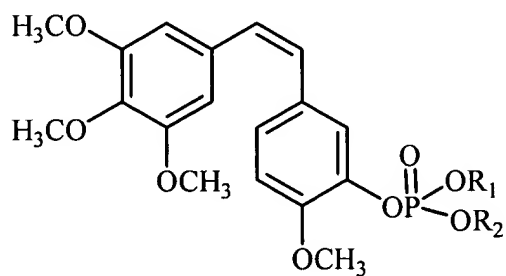
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alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic, or any combination thereof.

34. (Previously presented) A pharmaceutical composition comprising the compound of claim 31 and a pharmaceutically acceptable carrier thereof.
35. (Previously presented) A pharmaceutical composition comprising the compound of claim 33 and a pharmaceutically acceptable carrier thereof.
36. (Cancelled)
37. (Currently amended) A method of modulating tumor growth or metastasis in an animal comprising the administration of an effective amount of a compound having a general structure of the formula VI:



(VI)

wherein:

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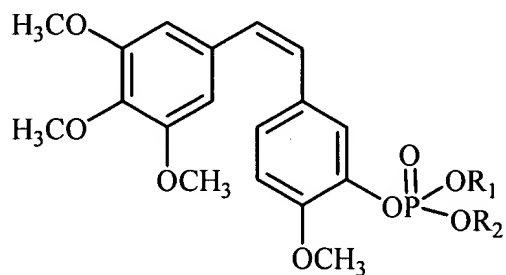
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one of  $-OR_1$  or  $-OR_2$  is  $O^+Q^-$  or  $-O-Q$ , and the other is hydroxyl,  $-O^+Q^-$ , or  $-O-Q$ ; and

Q is an alkali metal other than sodium or potassium, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic or any combination thereof.

38. (Previously presented) The method of claim 37, wherein Q is a metal selected from the group consisting of lithium, cesium, manganese, magnesium, calcium, and zinc.
39. (Previously presented) The method of claim 37, wherein Q is a heteroarylene or a heterocyclyl selected from the group consisting of imidazole, morpholine, piperazine, piperidine, pyrazole, and pyridine.
40. (Previously presented) A method of modulating microbial growth in an animal comprising the administration of an effective amount of a compound having a general structure of the formula VI:



(VI)

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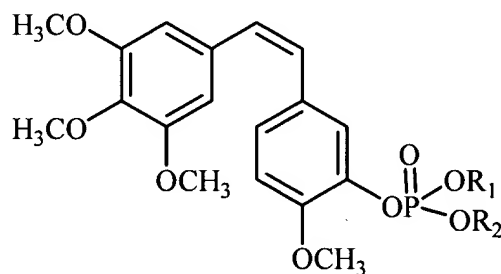
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wherein:

one of  $-OR_1$  or  $-OR_2$  is  $O^-Q^+$  or  $-O-Q$ , and the other is hydroxyl,  $-O^-Q^+$ , or  $-O-Q$ ; and

Q is an alkali metal, an alkali earth metal, a transition metal, a heteroarylene, a heterocyclyl, a nucleoside, a nucleotide, an alkaloid, an amino-sugar, an amino-nitrile, or a nitrogen-containing antibiotic or any combination thereof.

41. (Previously presented) A process for preparing a compound of Formula VI



(VI)

wherein one of  $R_1$  or  $R_2$  is sodium and the other is sodium or hydrogen,

the process comprising:

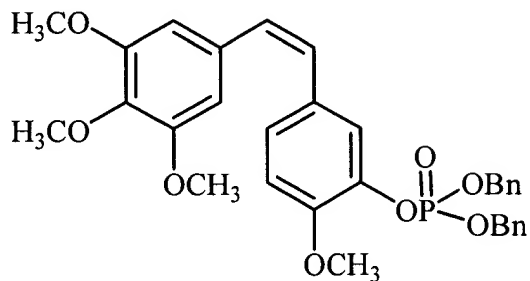
- (a) contacting *cis*-combretastatin A-4 in a solvent with di(benzyl)phosphite in the presence of tetrahalomethane, a tertiary amine, and an acylation catalyst to form a protected phosphate ester of Formula IV;

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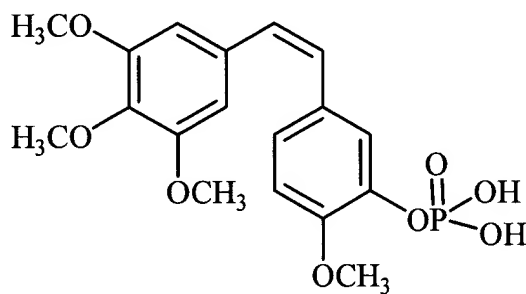
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(IV)

(b) contacting the protected phosphate ester of Formula IV with a trialkylhalo silane for a period of time sufficient to generate the phosphoric acid compound of Formula V; and



(V)

(c) contacting the phosphoric acid compound of Formula V with an alkali metal hydroxide, alkali metal alkoxide, or a salt thereof to generate a compound of Formula VI.